

```

chain nodes :
1  2  3  4  5  6  7  9  10
chain bonds :
1-2  1-3  1-4  1-5  1-6  1-7  6-9  7-10
exact/norm bonds :
6-9  7-10
exact bonds :
1-2  1-3  1-4  1-5  1-6  1-7

```

G1:Ca,K,Li,Mg,Na,Cb,Ak

```

Match level :
1:CLASS  2:CLASS  3:CLASS  4:CLASS  5:CLASS  6:CLASS  7:CLASS  9:CLASS  10:CLASS

```

L1 STRUCTURE UPLOADED

=> d his

(FILE 'HOME' ENTERED AT 18:44:21 ON 05 MAY 2008)

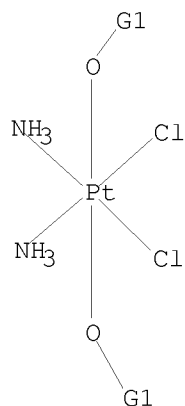
FILE 'REGISTRY' ENTERED AT 18:44:35 ON 05 MAY 2008

L1 STRUCTURE UPLOADED

=> d l1

L1 HAS NO ANSWERS

L1 STR



G1 Ca,K,Li,Mg,Na,Cb,Ak

Structure attributes must be viewed using STN Express query preparation.

=> s l1

SAMPLE SEARCH INITIATED 18:44:56 FILE 'REGISTRY'

SAMPLE SCREEN SEARCH COMPLETED - 166 TO ITERATE

100.0% PROCESSED 166 ITERATIONS

3 ANSWERS

SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE \*\*COMPLETE\*\*

BATCH \*\*COMPLETE\*\*

PROJECTED ITERATIONS: 2547 TO 4093

PROJECTED ANSWERS: 3 TO 162

L2 3 SEA SSS SAM L1

=> s l1 full

FULL SEARCH INITIATED 18:45:02 FILE 'REGISTRY'

FULL SCREEN SEARCH COMPLETED - 2996 TO ITERATE

100.0% PROCESSED 2996 ITERATIONS

68 ANSWERS

SEARCH TIME: 00.00.01

L3 68 SEA SSS FUL L1

=> fil caplus

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

178.36

178.57

FILE 'CAPLUS' ENTERED AT 18:45:09 ON 05 MAY 2008

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FILE LAST UPDATED: 4 May 2008 (20080504/ED)

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<http://www.cas.org/infopolicy.html>

=> s 13

L4 22 L3

=> d 1-22 bib abs

L4 ANSWER 1 OF 22 CAPLUS COPYRIGHT 2008 ACS on STN  
AN 2007:1373074 CAPLUS  
DN 148:181734  
TI Novel Di- and Tetracarboxylatoplatinum(IV) Complexes. Synthesis, Characterization, Cytotoxic Activity, and DNA Platination  
AU Reithofer, Michael R.; Valiahdi, Seied M.; Jakupec, Michael A.; Arion, Vladimir B.; Egger, Alexander; Galanski, Markus; Keppler, Bernhard K.  
CS Institute of Inorganic Chemistry, University of Vienna, Vienna, A-1090, Austria  
SO Journal of Medicinal Chemistry (2007), 50(26), 6692-6699  
CODEN: JMCMAR; ISSN: 0022-2623  
PB American Chemical Society  
DT Journal  
LA English  
OS CASREACT 148:181734  
AB Octahedrally configured diaminedichloro- and diamineoxalatoplatinum(IV) complexes with axial hydroxo ligands were carboxylated with succinic or glutaric anhydride. The free, uncoordinated carboxylic acid groups were further derivatized with amines and alcs. to the resp. amides and esters and characterized in detail by elemental anal., mass spectrometry, and multinuclear (1H, 13C, 15N, and 195Pt) NMR spectroscopy. Cytotoxicity of the complexes was studied in four human cancer cell lines derived from ovarian carcinoma (CH1, SK-OV-3), cervical carcinoma (HeLa), and colon carcinoma (SW480) by the MTT assay. Structure-activity relations revealed a low activity for Pt complexes with underivatized carboxylic acid moieties and amide derivs. displaying the hydroxyethylamino residue. Within amides, cyclopentylamino analogs were equipped with the highest cytotoxic potential. However, ester derivs. yielded IC50 values mostly in the low micromolar range and comparable to those of cisplatin. DNA platination studies of selected complexes revealed a high DNA platination capacity in parallel to a high cytotoxic potential and vice versa.

L4 ANSWER 2 OF 22 CAPLUS COPYRIGHT 2008 ACS on STN  
AN 2007:1203726 CAPLUS  
DN 148:23931  
TI Reduction of cis,trans,cis-[PtCl2(OCOCH3)2(NH3)2] by Aqueous Extracts of Cancer Cells  
AU Nemirovski, Alina; Kasherman, Yonit; Tzaraf, Yael; Gibson, Dan  
CS Department of Medicinal Chemistry and Natural Products, School of Pharmacy, The Hebrew University of Jerusalem, Jerusalem, 91120, Israel  
SO Journal of Medicinal Chemistry (2007), 50(23), 5554-5556  
CODEN: JMCMAR; ISSN: 0022-2623  
PB American Chemical Society  
DT Journal

LA English  
AB Pt(IV) complexes must be reduced to kill cancer cells. While reduction rates correlate with reduction potentials, we wanted to check if the rates of reduction depend on the cell line used. The reduction of cis,trans,cis-[PtCl<sub>2</sub>(OCOCH<sub>3</sub>)<sub>2</sub>(NH<sub>3</sub>)<sub>2</sub>] by exts. of three cell lines was measured, and the rates follow the order A2780cisR > A2780 > HT-29. The reduction is not carried out by the low mol. weight (MW) antioxidants but primarily by cellular components with MW > 3000.  
RE.CNT 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 22 CAPLUS COPYRIGHT 2008 ACS on STN  
AN 2007:1080753 CAPLUS  
DN 147:527837  
TI Calculation of Lipophilicity of a Large, Diverse Dataset of Anticancer Platinum Complexes and the Relation to Cellular Uptake  
AU Oldfield, Steven P.; Hall, Matthew D.; Platts, James A.  
CS School of Chemistry, Cardiff University, Cardiff, CF10 3AT, UK  
SO Journal of Medicinal Chemistry (2007), 50(21), 5227-5237  
CODEN: JMCMAR; ISSN: 0022-2623  
PB American Chemical Society  
DT Journal  
LA English  
AB A quant. structure-property relationship (QPSR) for the octanol-water partition of platinum complexes was constructed using mol. descriptors derived from d. functional (DFT) calcns. A dataset of partition data for 64 complexes, consisting of 43 square-planar platinum(II) and 21 octahedral platinum(IV) complexes, was drawn from literature sources. Not only does this dataset include considerable structural diversity of complexes considered but also a variety of techniques for the measurement of partition coeffs. These data were modeled using descriptors drawn from electrostatic potentials and hardness/softness indexes projected onto mol. surfaces. This required initial descriptor selection using a genetic algorithm approach, followed by partial least-squares regression against log Po/w data. In this way, a statistically robust model was constructed, with errors of similar size to the variation in log Po/w from multiple exptl. measurements. Implications of lipophilicity for cellular accumulation of Pt-based drugs, and hence for design of new drugs, are discussed, as is the uptake of metabolites of cisplatin.  
RE.CNT 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 22 CAPLUS COPYRIGHT 2008 ACS on STN  
AN 2007:1012725 CAPLUS  
DN 148:85278  
TI Conjugated Platinum(IV)-Peptide Complexes for Targeting Angiogenic Tumor Vasculature  
AU Mukhopadhyay, Sumitra; Barnes, Carmen M.; Haskel, Ariel; Short, Sarah M.; Barnes, Katie R.; Lippard, Stephen J.  
CS Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA, 02139, USA  
SO Bioconjugate Chemistry (2008), 19(1), 39-49  
CODEN: BCCHES; ISSN: 1043-1802  
PB American Chemical Society  
DT Journal  
LA English  
AB The integrins  $\alpha\beta3$  and  $\alpha\beta5$  and the membrane-spanning surface protein aminopeptidase N (APN) are highly expressed in tumor-induced angiogenesis, making them attractive targets for therapeutic intervention. Both integrins and APN recognize a broad range of peptides containing RGD (Arg-Gly-Asp) and NGR (Asn-Gly-Arg) motifs,

resp. Here, we describe the design, synthesis, and characterization of a series of mono- and difunctionalized platinum(IV) complexes in which a conjugated peptide motif, containing RGD, (CRGDC)<sub>c</sub>, (RGDfK)<sub>c</sub>, or NGR, is appended as a "tumor-homing device" to target tumor endothelial cells selectively over healthy cells. Platinum(IV)-peptide complexes with nonspecific amino acids or peptide moieties were prepared as controls. Concentration-response curves of these compds. were evaluated against primary proliferating endothelial cells and tumor cell lines and compared to those of cisplatin, a well-described platinum-based chemotherapeutic agent. The Pt(IV)-RGD conjugates were highly and specifically cytotoxic to cell lines containing  $\alpha v\beta 3$  and  $\alpha v\beta 5$ , approaching the activity of cisplatin. The Pt(IV)-NGR complexes were less active than Pt(IV)-RGD-containing compds. but more active than nonspecific Pt-peptide controls. Integrin  $\alpha v\beta 3$  mediated, at least in part, the anti-proliferative effect of a Pt(IV)-RGD conjugate, as demonstrated by a decreased inhibitory response when endothelial cells were either (1) incubated with an excess of  $\alpha v\beta 3/\alpha v\beta 5$ -specific RGD pentapeptides or (2) transfected with RNAi for  $\beta 3$ , but not  $\beta 1$ , integrins. These results suggest a rational approach to improved chemotherapy with Pt(IV)-peptide conjugates by selective drug delivery to the tumor compartment.

RE.CNT 51        THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD  
                  ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4    ANSWER 5 OF 22    CAPLUS    COPYRIGHT 2008 ACS on STN  
 AN    2007:646516    CAPLUS  
 DN    147:242935  
 TI    Soluble Single-Walled Carbon Nanotubes as Longboat Delivery Systems for Platinum(IV) Anticancer Drug Design  
 AU    Feazell, Rodney P.; Nakayama-Ratchford, Nozomi; Dai, Hongjie; Lippard, Stephen J.  
 CS    Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA, 02139, USA  
 SO    Journal of the American Chemical Society (2007), 129(27), 8438-8439  
       CODEN: JACSAT; ISSN: 0002-7863  
 PB    American Chemical Society  
 DT    Journal  
 LA    English  
 AB    Amine-functionalized soluble single-walled carbon nanotubes (SWNTs) were derivatized with cisplatin prodrug conjugates as a delivery system by which to internalize multiple prodrug centers. The platinum(IV) complex, c,c,t-[Pt(NH<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>(OEt)(O<sub>2</sub>CCH<sub>2</sub>CH<sub>2</sub>CO<sub>2</sub>H)], was tethered to the surface of the carbon nanotubes through peptide linkages formed by the reaction of the SWNT-tethered amines with the carboxylate moiety. The SWNTs were taken into testicular cancer cells by endocytosis, where the drop in pH facilitates reductive release of the platinum(II) core complex, which then readily diffuses throughout the cell, as determined by platinum atomic absorption spectroscopy. The entrapment of the SWNTs within the endosomes was confirmed by fluorescence microscopy of SWNTs containing both tethered fluorescein and platinum units. The cytotoxicity of the free platinum(IV) complex increases by >100-fold when the complex is attached to the surface of the functionalized SWNTs.

RE.CNT 23        THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD  
                  ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4    ANSWER 6 OF 22    CAPLUS    COPYRIGHT 2008 ACS on STN  
 AN    2006:599431    CAPLUS  
 DN    146:324  
 TI    The fate of platinum(II) and platinum(IV) anti-cancer agents in cancer cells and tumors  
 AU    Hall, Matthew D.; Alderden, Rebecca A.; Zhang, Mei; Beale, Philip J.; Cai,

Zhonghou; Lai, Barry; Stampfl, Anton P. J.; Hambley, Trevor W.  
 CS Centre for Heavy Metals Research, School of Chemistry F11, The University  
 of Sydney, NSW 2006, Australia  
 SO Journal of Structural Biology (2006), 155(1), 38-44  
 CODEN: JSBIEM; ISSN: 1047-8477  
 PB Elsevier  
 DT Journal  
 LA English  
 AB SRIXE mapping has been used to gain insight into the fate of platinum(II)  
 and platinum(IV) complexes in cells and tumors treated with anticancer  
 active complexes to facilitate the development of improved drugs. SRIXE  
 maps were collected of thin sections of human ovarian (A2780) cancer cells  
 treated with bromine containing platinum complexes, cis-[PtCl<sub>2</sub>(3-Brpyr)(NH<sub>3</sub>)]  
 (3-Brpyr = 3-bromopyridine) and cis,trans,cis-[PtCl<sub>2</sub>(OAcBr)<sub>2</sub>(NH<sub>3</sub>)<sub>2</sub>] (OAcBr  
 = bromoacetate), or a platinum complex with an intercalator attached  
 cis-[PtCl<sub>2</sub>(2-[(3-aminopropyl)amino]-9,10-anthracenedione)(NH<sub>3</sub>)]. After 24  
 h the complexes appear to be localized in the cell nucleus with a lower  
 concentration in the surrounding cytoplasm. In cells treated with  
 cis-[PtCl<sub>2</sub>(3-Brpyr)(NH<sub>3</sub>)] the concentration of bromine was substantially higher  
 than in control cells and the bromine was co-localized with the platinum  
 consistent with the 3-bromopyridine ligand remaining bound to the  
 platinum. The cells treated with cis,trans,cis-[PtCl<sub>2</sub>(OAcBr)<sub>2</sub>(NH<sub>3</sub>)<sub>2</sub>] also  
 showed an increased level of bromine, but to a much lesser extent than for  
 those treated with cis-[PtCl<sub>2</sub>(3-Brpyr)(NH<sub>3</sub>)] suggestive of substantial  
 reduction of the platinum(IV) complex. Maps were also collected from thin  
 sections of a 4T1.2 neo 1 mammary tumor xenograft removed from a mouse 3 h  
 after treatment with cis,trans,cis-[PtCl<sub>2</sub>(OH)<sub>2</sub>(NH<sub>3</sub>)<sub>2</sub>] and revealed  
 selective uptake of platinum by one cell.

RE.CNT 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 22 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2005:1163378 CAPLUS  
 DN 144:63383  
 TI Synthesis and Characterization of Platinum(IV) Anticancer Drugs with  
 Functionalized Aromatic Carboxylate Ligands: Influence of the Ligands on  
 Drug Efficacies and Uptake  
 AU Ang, Wee Han; Pilet, Sebastien; Scopelliti, Rosario; Bussy, Francois;  
 Juillerat-Jeanneret, Lucienne; Dyson, Paul J.  
 CS Institut des Sciences et Ingenierie Chimiques, Ecole Polytechnique  
 Federale de Lausanne (EPFL), Lausanne, CH 1015, Switz.  
 SO Journal of Medicinal Chemistry (2005), 48(25), 8060-8069  
 CODEN: JMCMAR; ISSN: 0022-2623  
 PB American Chemical Society  
 DT Journal  
 LA English  
 OS CASREACT 144:63383  
 AB Trans-Pt(IV) complexes with functionalized aromatic carboxylate ligands,  
 cis,cis,trans-Pt(NH<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>(CO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>R)<sub>2</sub> (R = H (3), p-vinyl (4), p-methoxy  
 (5), p-iodo (6), p-cyano (7), or o-carboxyl (8)) was synthesized and  
 characterized by spectroscopic methods. Crystal structures of 3, 4, 7,  
 and 8 were obtained, which revealed that their structural conformations  
 were influenced by intramol. H-bonding interactions. The complexes were  
 evaluated for cellular uptake and inhibition of cell proliferation against  
 a panel of lung, colon, and breast carcinoma cell lines. The  
 functionalization of the aromatic carboxylate ligand has a profound influence  
 on the uptake, and hence, efficacy, of this class of complex.

RE.CNT 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 8 OF 22 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2005:1014223 CAPLUS

DN 143:359627  
 TI The influence of tumor microenvironmental factors on the efficacy of  
 cisplatin and novel platinum(IV) complexes  
 AU Mellor, H. R.; Snelling, S.; Hall, M. D.; Modok, S.; Jaffar, M.; Hambley,  
 T. W.; Callaghan, R.  
 CS Oxford Drug Resistance Group, Nuffield Department of Clinical Laboratory  
 Sciences, John Radcliffe Hospital, University of Oxford, Oxford, OX3 9DU,  
 UK  
 SO Biochemical Pharmacology (2005), 70(8), 1137-1146  
 CODEN: BCPA6; ISSN: 0006-2952  
 PB Elsevier B.V.  
 DT Journal  
 LA English  
 AB The chemotherapeutic drug cisplatin is an important treatment for many  
 types of solid tumors, in particular non-small cell lung cancer (NSCLC).  
 Platinum(IV) complexes offer several advantages to cisplatin due to their  
 requirement for reduction to the active platinum(II) form to elicit  
 cytotoxicity. This should minimize non-specific effects and facilitate  
 higher amts. of the active complexes reaching the target DNA. Hypoxia and  
 a quiescent cell population are features of the tumor microenvironment  
 known to lead to resistance to many chemotherapeutic agents. It is  
 unclear how these microenvironmental factors will impact on the efficacy  
 of novel platinum(IV) complexes. Consequently, the cytotoxicities of  
 several platinum drugs were determined in monolayer and tumor spheroid cultures  
 derived from NSCLC lines. Platinum(IV) reduction potential correlated well  
 with cytotoxicity. The complex containing a chloro axial ligand demonstrated  
 the greatest potency and the drug with the hydroxy ligand was the least  
 effective. Although drug cytotoxicity was not enhanced under hypoxic  
 conditions, both cisplatin and the platinum(IV) complexes retained full  
 potency. In addition, all of the platinum drugs retained the ability to  
 evoke apoptosis in quiescent cells. In summary, unlike many anticancer  
 drugs, the platinum(IV) complexes retain cytotoxic potency under  
 resistance-inducing tumor microenvironmental conditions and warrant  
 further investigation as more selective alternatives to current  
 platinum-based therapy for the treatment of solid tumors.

RE.CNT 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 9 OF 22 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2005:395221 CAPLUS  
 DN 142:441848  
 TI Method for the preparation of trans- or cis-diammoniumdichlorodihydroxopla  
 tinum (IV), and use for the treatment of cancer  
 IN Salama, Zoser B.  
 PA Germany  
 SO PCT Int. Appl., 50 pp.  
 CODEN: PIXXD2  
 DT Patent  
 LA German

FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2005040045	A2	20050506	WO 2004-DE2296	20041013
	WO 2005040045	A3	20050707		
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
	RW:	BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,			

EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE,  
SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE,  
SN, TD, TG

EP 1524273 A1 20050420 EP 2003-90344 20031013  
EP 1524273 B1 20061122

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,  
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK

AU 2004283125 A1 20050506 AU 2004-283125 20041013  
CA 2565096 A1 20050506 CA 2004-2565096 20041013  
EP 1678189 A2 20060712 EP 2004-789998 20041013  
EP 1678189 B1 20070321

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,  
IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK

CN 1867573 A 20061122 CN 2004-80029889 20041013  
BR 2004015295 A 20061226 BR 2004-15295 20041013  
JP 2007513066 T 20070524 JP 2006-534580 20041013  
MX 2006PA03843 A 20070202 MX 2006-PA3843 20060406  
IN 2006DN02642 A 20070810 IN 2006-DN2642 20060511  
US 20070286905 A1 20071213 US 2007-595400 20070202

PRAI EP 2003-90344 A 20031013  
US 2003-512097P P 20031020  
WO 2004-DE2296 W 20041013

OS MARPAT 142:441848

AB The invention relates to a method for the production of trans- or  
cis-diammoniumdichlorodihydroxoplatinum (IV) and derivs. thereof. Trans-  
or cis-diammoniumdichloroplatinum (II) is reacted with a solution containing  
>30%

peroxide at temps. below 30°C, the product obtained thereby is  
dissolved with a mineral acid and finally precipitated with an alkaline  
solution The  
comps. of the invention are useful as therapeutic agents for the  
treatment of e.g. cancer.

L4 ANSWER 10 OF 22 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2005:31552 CAPLUS

DN 142:273345

TI Rational Design of Platinum(IV) Compounds to Overcome Glutathione-S-  
Transferase Mediated Drug Resistance

AU Ang, Wee Han; Khalaila, Isam; Allardyce, Claire S.; Juillerat-Jeanneret,  
Lucienne; Dyson, Paul J.

CS Institut des Sciences et Ingenierie Chimiques, Ecole Polytechnique  
Federale de Lausanne EPFL-BCH, Lausanne, CH 1015, Switz.

SO Journal of the American Chemical Society (2005), 127(5), 1382-1383  
CODEN: JACSAT; ISSN: 0002-7863

PB American Chemical Society

DT Journal

LA English

AB A rationally designed Pt(IV) anticancer compound is described, employing the  
novel concept of tethering an inhibitor of glutathione-S-transferase, an  
enzyme associated with Pt-based drug-resistance, to cisplatin. Its enzyme  
inhibition activity, investigated using spectrophotometric and mass  
spectrometry-based techniques, and cytotoxic profile in resistant cancer  
cells are described.

RE.CNT 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 11 OF 22 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2004:1019754 CAPLUS

DN 141:419813

TI Coordination complexes having tethered therapeutic agents and/or targeting  
moieties, and methods of making and using the same

IN Lippard, Stephen J.; Barnes, Carmen M.; Haskel, Ariel; Barnes, Katie R.



FAN.CNT 1

GI



AB In part, the present invention is directed to coordination complexes comprising a therapeutic agent. Claimed is a compound comprising: (a) a Pt metal center (b) two cis labile ligands bonded to the Pt, and (c) one or more therapeutic agents and/or targeting moieties covalently attached to the Pt, wherein the therapeutic agent is not covalently attached to the Pt center through the cis labile ligands. The two cis labile ligands may be halides, the therapeutic agent may be a steroid, e.g., estrogen, and the targeting moiety may be a peptide. The compds. include cis,cis,trans complexes I (X = labile covalently bonded ligand, or X2 = bidentate ligand; L = ligand covalently bonded to Pt center, or L2 = bidentate ligand; M = therapeutic agent, targeting moiety, or labile covalently bonded ligand; R = therapeutic agent or targeting moiety). Example complexes prepared are cisplatin derivs. II (R' = Q, n = 1-5) containing estradiol-3-benzoate tethered to the Pt and peptide-tethered derivs. II (R' = peptide, e.g., NGRNH-, AGRNH-, and biotin-labeled derivs.). Reduction of the Pt(IV) complexes to Pt(II) releases the therapeutic agent or targeting moiety to be therapeutically effective for treatment of cancer cells which comprise a receptor for the agent/moiety, especially where the

therapeutic agent causes increased expression of HMG or the cancer cells express estrogen ER(+) receptors. Cytotoxicities of compds. II against MCF-7 and HCC-1937 cell lines were studied. Also claimed is a kit comprising the compds. and instructions for administering the compound to a patient.

RE.CNT 116 THERE ARE 116 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 12 OF 22 CAPLUS COPYRIGHT 2008 ACS on STN  
AN 2004:819575 CAPLUS  
DN 142:361  
TI The mechanism of action of platinum(IV) complexes in ovarian cancer cell lines  
AU Hall, Matthew D.; Amjadi, Shahriar; Zhang, Mei; Beale, Philip J.; Hambley, Trevor W.  
CS Centre for Heavy Metals Research, School of Chemistry, University of Sydney, Sydney, NSW 2006, Australia  
SO Journal of Inorganic Biochemistry (2004), 98(10), 1614-1624  
CODEN: JIBIDJ; ISSN: 0162-0134  
PB Elsevier B.V.  
DT Journal  
LA English  
AB The reduction potentials, lipophilicities, cellular uptake and cytotoxicity have been examined for two series of platinum(IV) complexes that yield common platinum(II) complexes on reduction: cis-[PtCl<sub>4</sub>(NH<sub>3</sub>)<sub>2</sub>], cis,trans,cis-[PtCl<sub>2</sub>(OAc)<sub>2</sub>(NH<sub>3</sub>)<sub>2</sub>], cis,trans,cis-[PtCl<sub>2</sub>(OH)<sub>2</sub>(NH<sub>3</sub>)<sub>2</sub>], [PtCl<sub>4</sub>(en)], cis,trans-[PtCl<sub>2</sub>(OAc)<sub>2</sub>(en)] and cis,trans-[PtCl<sub>2</sub>(OH)<sub>2</sub>(en)] (en = ethane-1,2-diamine, OAc = acetate). As previously reported, the reduction occurs most readily when the axial ligand is chloride and least readily when it is hydroxide. The en series of complexes are marginally more lipophilic than their ammine analogs. The presence of axial chloride or acetate ligands results in a slighter higher lipophilicity compared with the platinum(II) analog whereas hydroxide ligands lead to a substantially lower lipophilicity. The cellular uptake is similar for the platinum(II) species and their analogous tetrachloro complexes, but is substantially lower for the acetato and hydroxo complexes, resulting in a correlation with the reduction potential. The activities are also correlated with the reduction potentials with the tetrachloro- complexes being the most active of the platinum(IV) series and the hydroxo- complexes being the least active. These results are interpreted in terms of reduction, followed by aquation reducing the amount of efflux from the cells resulting in an increase in net uptake.

RE.CNT 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 13 OF 22 CAPLUS COPYRIGHT 2008 ACS on STN  
AN 2004:324513 CAPLUS  
DN 140:385646  
TI Synthesis, Characterization, and Cytotoxicity of a Series of Estrogen-Tethered Platinum(IV) Complexes  
AU Barnes, Katie R.; Kutikov, Alexander; Lippard, Stephen J.  
CS Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA, 02139, USA  
SO Chemistry & Biology (2004), 11(4), 557-564  
CODEN: CBOLE2; ISSN: 1074-5521  
PB Cell Press  
DT Journal  
LA English  
OS CASREACT 140:385646  
AB Several estrogen-tethered platinum(IV) complexes were prepared and characterized by ESI-MS and 1H NMR spectroscopy. Their design was inspired by the observation that estrogen receptor-pos. cells exposed to

the hormone are sensitized to cisplatin. Intracellular reduction of bis-estrogen-cis-diamminedichloroplatinum(IV), BEPn (where n = 1-5 methylene groups between Pt and estrogen), occurs to afford cisplatin and two equivalent of the linker-modified estrogen. The ability of BEPn to induce overexpression of HMGB1 was established by immunofluorescence microscopy. The cytotoxicity of the compds. was evaluated in ER(+) MCF-7 and ER(-) HCC-1937 human breast cancer cell lines. BEP3 selectively induces overexpression of HMGB1 in MCF-7 cells, compared to HCC-1937 cells, and enhances their sensitivity (IC50 = 2.1±0.4 µM vs. 3.7±0.9 µM, resp.) to the compound. The difference in compound activities and the potential of compds. of this class for treating breast and ovarian cancer are discussed.

RE.CNT 39        THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD  
                 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4     ANSWER 14 OF 22   CAPLUS   COPYRIGHT 2008 ACS on STN

AN     2003:726129   CAPLUS

DN     140:192358

TI     The cellular distribution and oxidation state of platinum(II) and platinum(IV) antitumour complexes in cancer cells

AU     Hall, Matthew D.; Dillon, Carolyn T.; Zhang, Mei; Beale, Philip; Cai, Zhonghou; Lai, Barry; Stampfl, Anton P. J.; Hambley, Trevor W.

CS     School of Chemistry F11, Centre for Heavy Metals Research, The University of Sydney, 2006, Australia

SO     JBIC, Journal of Biological Inorganic Chemistry (2003), 8(7), 726-732  
CODEN: JJBCFA; ISSN: 0949-8257

PB     Springer-Verlag

DT     Journal

LA     English

AB     The cellular distribution of platinum in A2780 ovarian cancer cells treated with cisplatin and platinum(IV) complexes with a range of reduction potentials has been examined using elemental anal. (synchrotron radiation-induced x-ray emission). The cellular distribution of platinum(IV) drugs after 24 h is similar to that of cisplatin, consistent with the majority of administered platinum(IV) drugs being reduced. Micro-x-ray absorption near-edge spectra of cells treated with cisplatin and platinum(IV) complexes confirmed the reduction of platinum(IV) to platinum(II). In cells treated, the most difficult to reduce complex, cis,trans,cis-[PtCl2(OH)2(NH3)2], platinum(IV) was detected in the cells along with platinum(II). The observations are in accordance with the relative ease of reduction of the platinum(IV) complexes used and support the requirement of reduction for activation of platinum(IV) complexes.

RE.CNT 40        THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD  
                 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4     ANSWER 15 OF 22   CAPLUS   COPYRIGHT 2008 ACS on STN

AN     2003:415965   CAPLUS

DN     139:111256

TI     XANES Determination of the Platinum Oxidation State Distribution in Cancer Cells Treated with Platinum(IV) Anticancer Agents

AU     Hall, Matthew D.; Foran, Garry J.; Zhang, Mei; Beale, Philip J.; Hambley, Trevor W.

CS     Centre for Heavy Metals Research School of Chemistry, University of Sydney, Sydney, 2006, Australia

SO     Journal of the American Chemical Society (2003), 125(25), 7524-7525  
CODEN: JACSAT; ISSN: 0002-7863

PB     American Chemical Society

DT     Journal

LA     English

AB     Here the authors describe the use of x-ray absorption near edge spectroscopy (XANES) to provide information about the relative proportions of platinum(II) and platinum(IV) complexes by analyzing the XANES edge

height. The intracellular reduction of platinum(IV) complexes in cancer cells has been observed directly, and the proportion of reduction after 2 h was found to correlate with the reduction potentials of the complexes.

RE.CNT 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 16 OF 22 CAPLUS COPYRIGHT 2008 ACS on STN

AN 1999:228639 CAPLUS

DN 131:27016

TI Reduction of the anti-cancer drug analog cis,trans,cis-  
[PtCl<sub>2</sub>(OCOCH<sub>3</sub>)<sub>2</sub>(NH<sub>3</sub>)<sub>2</sub>] by L-cysteine and L-methionine and its crystal structure

AU Chen, Lie; Lee, Peng Foo; Ranford, John D.; Vittal, Jagadese J.; Wong, Siew Ying

CS Department of Chemistry, National University of Singapore, 119270, Singapore

SO Journal of the Chemical Society, Dalton Transactions: Inorganic Chemistry (1999), (8), 1209-1212

CODEN: JCDBTBI; ISSN: 0300-9246

PB Royal Society of Chemistry

DT Journal

LA English

AB Cis,trans,cis-[PtCl<sub>2</sub>(OCOCH<sub>3</sub>)<sub>2</sub>(NH<sub>3</sub>)<sub>2</sub>] (1) was synthesized as a simplified and more water-soluble model of the anticancer drug cis,trans,cis-[PtCl<sub>2</sub>(OCOCH<sub>3</sub>)<sub>2</sub>(NH<sub>3</sub>)(C<sub>6</sub>H<sub>11</sub>NH<sub>2</sub>)] (JM 216). The crystal structure of 1 shows an octahedral coordination sphere around the Pt(IV) with strong intramol. and weak intermol. H bonding. The kinetics of reduction of 1 by the divalent S amino acids L-cysteine and L-methionine was determined over a range of pH values by multinuclear NMR. The reduction is strongly pH dependent, being related to the protonation state of the amino acid and the basicity of the S. Reduction rates are dramatically slower than for previous models of Pt(IV) drug systems.

RE.CNT 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 17 OF 22 CAPLUS COPYRIGHT 2008 ACS on STN

AN 1999:60503 CAPLUS

DN 131:279

TI Synthesis, characterization and DNA modification induced by a novel Pt(IV)-bis(monoglutarate) complex which induces apoptosis in glioma cells

AU Perez, J. M.; Camazon, M.; Alvarez-Valdes, A.; Quiroga, A. G.; Kelland, L. R.; Alonso, C.; Navarro-Ranninger, M. C.

CS Facultad de Ciencias, Departamento de Quimica Inorganica, Universidad Autonoma de Madrid, Madrid, 28049, Spain

SO Chemico-Biological Interactions (1999), 117(2), 99-115

CODEN: CBINA8; ISSN: 0009-2797

PB Elsevier Science Ireland Ltd.

DT Journal

LA English

AB Programmed cell death or apoptosis is a mechanism for the elimination of cells that occurs not only in physiol. processes but also in drug-induced tumor cell death. Thus, because cisplatin, cis-diamminechloroplatinum (II), produces important damages on the DNA inducing apoptosis in several cell lines it has become a widely used antitumor drug. However, cisplatin possesses some dose-limiting toxicities mainly nephrotoxicity. Pt(IV) complexes, such as iproplatin, ormaplatin, and JM216 are a new class of platinum complexes that exhibits less toxicity than cisplatin. Some of these complexes have shown significant antitumor activity and a low cross-resistance to cisplatin. In the present paper, we have analyzed the DNA binding mode and the cytotoxicity of a novel Pt(IV)-bis(monoglutarate) complex. The data show that this novel complex produces DNA interstrand cross-links to a higher extent and with a faster kinetics

than cisplatin. Also the Pt(IV)-bis (monoglutarate) complex kills glioma cells at drug concns. significantly lower than those of cisplatin. Interestingly, this Pt(IV) complex produces in the glioma cells characteristic features of apoptosis such as 'DNA laddering' and fragmented nuclei. Moreover, the p53 protein accumulates early in glioma cells as a result of Pt(IV)-bis (monoglutarate) treatment. These data indicate that the Pt(IV)-bis (monoglutarate) complex induces apoptosis in glioma cells through a p53-dependent pathway.

RE.CNT 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 18 OF 22 CAPLUS COPYRIGHT 2008 ACS on STN  
AN 1997:683909 CAPLUS  
DN 127:354661  
TI Synthesis of cisplatin diacetate  
AU Liu, Xinyong; Wang, Huicai; Wang, Chengyi; Tian, Jinguo; Ren, Jian  
CS Dep. Pharm., Shandong Med. Univ., Jinan, 250012, Peop. Rep. China  
SO Zhongguo Yiyao Gongye Zazhi (1997), 28(1), 11-12  
CODEN: ZYGZEA; ISSN: 1001-8255  
PB Zhongguo Yiyao Gongye Zazhi Bianjibu  
DT Journal  
LA Chinese  
AB Cisplatin diacetate, Pt(NH3)2Cl2(OAc)2, was prepared from cisplatin by oxidation with H2O2 in acetone to give the dihydroxy precursor, followed by O-acetylation with Ac2O.

L4 ANSWER 19 OF 22 CAPLUS COPYRIGHT 2008 ACS on STN  
AN 1996:121447 CAPLUS  
DN 124:192389  
TI Carboxylation of Dihydroxoplatinum(IV) Complexes via a New Synthetic Pathway  
AU Galanski, M.; Keppler, B. K.  
CS Anorganisch-Chemisches Institut, Universitaet Heidelberg, Heidelberg, D-69120, Germany  
SO Inorganic Chemistry (1996), 35(6), 1709-11  
CODEN: INOCAJ; ISSN: 0020-1669  
PB American Chemical Society  
DT Journal  
LA English  
AB The carboxylation of hydroxide coordinated to Pt(IV) by acyl chlorides to form the corresponding Pt(IV) carboxylates is described. Compds., Pt(IV)A2X2Y2, with A2 = diammine, ethanediamine and cis-cyclohexanediamine, X2 = dichloro, cyclobutane-1,1-dicarboxylato or malonato and Y = dodecanoato, tetradecanoato, hexadecanoato, octadecanoato, adamantanecarboxylato and acetylsalicylato, were synthesized and characterized by elemental anal., IR and NMR spectroscopic techniques. This new procedure in synthetic inorg. chemical can be transferred to a wide variety of trans-dicarboxylatoplatinum(IV) compds. which would be difficult to prepare by substitution reactions.

L4 ANSWER 20 OF 22 CAPLUS COPYRIGHT 2008 ACS on STN  
AN 1992:187485 CAPLUS  
DN 116:187485  
OREF 116:31503a,31506a  
TI Ammine/amine platinum(IV) dicarboxylates: a novel class of platinum complex exhibiting selective cytotoxicity to intrinsically cisplatin-resistant human ovarian carcinoma cell lines  
AU Kelland, Lloyd R.; Murrer, Barry A.; Abel, George; Giandomenico, Christen M.; Mistry, Prakash; Harrap, Kenneth R.  
CS Drug Dev. Sect., Inst. Cancer Res., Belmont/Sutton/Surrey, SM2 5NG, UK  
SO Cancer Research (1992), 52(4), 822-8  
CODEN: CNREA8; ISSN: 0008-5472

DT Journal  
 LA English  
 AB Using a panel of six human ovarian carcinoma cell lines varying by two orders of magnitude in terms of cisplatin cytotoxicity, the authors investigated the in vitro antitumor activity of a series of novel alkylamine ammine dicarboxylatodichloroplatinum (IV) complexes of the general formula  $c,t,c-[PtCl_2(OCOR_1)_2NH_3(RNH_2)]$ ; R and R<sub>1</sub> = aliphatic, aromatic or alicyclic. A clear relationship existed between increasing the number of carbons in the R<sub>1</sub> substituent and increasing cytotoxicity up to R<sub>1</sub> = C<sub>5</sub>H<sub>11</sub>. In terms of changing the R group, maximum cytotoxic effects were conferred by alicyclic substituents. Furthermore, increasing the alicyclic ring size from cyclobutane through to cycloheptane resulted in increasing cytotoxicity. The agents with longer axial chains (e.g., JM300, R = cyclohexyl, R<sub>1</sub> = C<sub>6</sub>H<sub>13</sub>) were more cytotoxic than cisplatin and, moreover, exhibited a selective cytotoxic effect against the most intrinsically cisplatin-resistant cell lines. The carboxylates JM221 (R = cyclohexyl, R<sub>1</sub> = C<sub>3</sub>H<sub>7</sub>) and JM244 (R = Pr, R<sub>1</sub> = C<sub>6</sub>H<sub>5</sub>) also retained activity against a 4-fold cisplatin-acquired resistant variant of the 41M cell line. At least part of the increased cytotoxicity of the dicarboxylate, JM221, over cisplatin appeared to be attributable to an increased intracellular accumulation. This novel class of platinum compound represents a valuable lead in the development of a "third-generation" agent capable of exhibiting activity against clin. disease currently resistant to cisplatin.

L4 ANSWER 21 OF 22 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 1990:584699 CAPLUS  
 DN 113:184699  
 OREF 113:31083a,31086a  
 TI Pt (IV) complexes as antitumor agents  
 IN Abrams, Michael J.; Gaindomenico, Christen M.; Murrer, Barry A.; Vollano, Jean F.  
 PA Johnson Matthey, Inc., USA  
 SO Eur. Pat. Appl., 21 pp.  
 CODEN: EPXXDW  
 DT Patent  
 LA English  
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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PI	EP 328274	A1	19890816	EP 1989-300787	19890127
	EP 328274	B1	19941019		
	R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
	ES 2063119	T3	19950101	ES 1989-300787	19890127
	IL 89119	A	19940412	IL 1989-89119	19890130
	KR 147270	B1	19980817	KR 1989-1069	19890131
	AU 8928971	A	19890803	AU 1989-28971	19890201
	AU 618310	B2	19911219		
	CA 1340286	C	19981222	CA 1989-589796	19890201
	DK 8900491	A	19890803	DK 1989-491	19890202
	DK 175050	B1	20040510		
	FI 8900512	A	19890803	FI 1989-512	19890202
	FI 91260	B	19940228		
	FI 91260	C	19940610		
	NO 8900426	A	19890803	NO 1989-426	19890202
	NO 177569	B	19950703		
	NO 177569	C	19951011		
	HU 49890	A2	19891128	HU 1989-522	19890202
	HU 205767	B	19920629		
	JP 01294684	A	19891128	JP 1989-24751	19890202
	ZA 8900831	A	19891227	ZA 1989-831	19890202
	US 5072011	A	19911210	US 1990-602931	19901025

US 5244919 A 19930914 US 1991-723971 19910701  
 PRAI US 1988-151674 A 19880202  
 US 1989-296776 A 19890113  
 US 1990-602931 A3 19901025  
 OS MARPAT 113:184699  
 AB Pt(IV) complexes, AA1 Pt(OCOR1)2X2 where A, A1 = NH3 or NH2, R, R1 = H, alkyl, alkenyl, aryl, aralkyl, alkylamino, or alkoxy or their derivs., and X = halogen or alkylmono- or -dicarboxylate as antitumor agents. Many of these complexes are soluble in both water and organic solvents, and this dual solubility might contribute to the high antitumor activity. Thus, cis-trans-cis-PtCl2(O2CH)2NH3(cyclohexylamine) was prepared by formylation of cis-trans-cis-PtCl2(OH)2NH3(cyclohexyl-NH2) in HCOOH during heating at 50°. The antitumor activity of some of these compds. was demonstrated and their LD50 and ED90 values (i.p. and oral) are tabulated.

L4 ANSWER 22 OF 22 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 1984:582625 CAPLUS  
 DN 101:182625  
 OREF 101:27469a,27472a  
 TI Study of the interaction of iminodiacetic acid with some complexes of platinum(IV) compounds  
 AU Al-Ansari, S. V.  
 CS USSR  
 SO Deposited Doc. (1982), VINITI 3676-83, 344-6 Avail.: VINITI  
 DT Report  
 LA Russian  
 AB Iminodiacetic acid (H2L) reacted with K2PtCl6, K2PtCl4(OH)2, and Pt(NH3)2Cl2(NO3)2 to give K[PtLC13], K2[Pt(HL)2Cl2(OH)2], and Pt(HL)2(NH3)2Cl2, resp.; Pt(HL)2(NH3)2(OH)2 was also prepared The complexes were characterized by IR and UV spectra, thermal decomposition studies, and potentiometric titrns. The ligand is tridentate in K[PtLC13] whereas in the other complexes it is monodentate.

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